

Acute Exposure to Environmental Tobacco Smoke and Heart Rate Variability

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Environmental tobacco smoke (ETS) has been associated with cardiovascular mortality. Pathophysiologic pathways leading from ETS exposure to cardiopulmonary disease are still being explored. Reduced cardiac autonomic function, as measured by heart rate variability (HRV), has been associated with cardiac vulnerability and may represent an important pathophysiologic mechanism linking ETS and risk of cardiac mortality. In this study we evaluated acute ETS exposure in a commercial airport with changes in HRV in 16 adult nonsmokers. We conducted ambulatory electrocardiographic (ECG) monitoring for 8-hr periods while participants alternated 2 hr in nonsmoking and smoking areas. Nicotine and respirable suspended particle concentrations and participants' blood oxygen saturation were also monitored. We calculated time and frequency domain measures of HRV for periods in and out of the smoking area, and we evaluated associations with ETS using comparative statistics and regression modeling. ETS exposure was negatively associated with all measures of HRV. During exposure periods, we observed an average decrement of approximately 12% in the standard deviation of all normal-to-normal heart beat intervals (an estimate of overall HRV). ETS exposures were not associated with mean heart rate or blood oxygen saturation. Altered cardiac autonomic function, assessed by decrements in HRV, is associated with acute exposure to ETS and may be part of the pathophysiologic mechanisms linking ETS exposure and increased cardiac vulnerability. **Key words:** autonomic function, cardiovascular disease, environmental tobacco smoke, heart rate variability, particulate matter, passive cigarette smoke. *Environ Health Perspect* 109:711–716 (2001). [Online 5 July 2001] <http://ehpnet1.niehs.nih.gov/docs/2001/7/abstract.html>

Exposure to environmental tobacco smoke (ETS) has been associated with cardiovascular disease and death (1–8). Potential pathophysiologic pathways leading from ETS exposure to cardiopulmonary disease are still being explored (5,9), but there has been a growing recognition of the importance of the autonomic nervous system in cardiovascular disease (10). Various measures of heart rate variability (HRV) evaluate changes in beat-to-beat interval durations using electrocardiography (ECG). These HRV measures, therefore, are noninvasive means to quantify the state of cardiac autonomic function. Reduced cardiac autonomic function, as measured by reduced HRV, has been associated with increased cardiac vulnerability (10–12). Is it possible that the autonomic nervous system plays a role in the pathophysiologic pathway between ETS exposure and cardiopulmonary disease?

Although various measures of HRV provide specific, well-defined, quantitative indicators of cardiac autonomic function (10), we know of no human studies that have evaluated the relationship between HRV and acute exposure to ETS. Studies have shown increases in HRV shortly after smoking cessation (13,14) and changes in heart rate (HR) (15) and HRV (16–18) associated

with acute exposure to respirable suspended particles (RSP), primarily of outdoor origin. Epidemiologic studies have also shown associations between exposure to RSP and cardiopulmonary disease similar to those observed with ETS (19–23).

The objective of this study was to evaluate potential effects of short-term ETS exposure on changes in cardiac autonomic function. Specifically, this study evaluated effects of short-term exposure to ETS in a commercial airport on cardiac autonomic function as measured by HR and HRV in a panel of adult nonsmokers. Associations with blood oxygen saturation and ETS were also evaluated.

Methods

Subject selection and study location. Sixteen research subjects were recruited using the following inclusion criteria: *a*) was 21 years of age or older; *b*) lived near Salt Lake City, Utah; and *c*) was willing to participate. Exclusion criteria included *a*) current smoker; *b*) cardiac transplant, cardiac pacemaker, or implantable defibrillator; *c*) health problems that exclude participation such as cold, flu, other infectious illness, Parkinsonism, chronic alcohol abuse, mental illness, or receiving oxygen therapy. Recruitment goals included

having a wide range of adult ages and approximately equal numbers of males and females. Research protocols and consent forms were approved by the institutional review board for human subjects at Brigham Young University. Before entering the study, all participants read and signed consent forms, then completed a questionnaire pertaining to background information, medical history, and prescription medications. Subjects received \$100 for participating in the study.

We obtained permission from management and security personnel to conduct this study at the Salt Lake City International Airport where smoking is allowed only in designated smoking areas. The study was conducted in the airport's C-concourse nonsmoking and smoking areas. The smoking area was enclosed, but it had see-through glass walls, nearly identical seating and lighting, and similar outside views of the tarmac in the foreground and the Wasatch mountains in the background.

Procedures at airport. Participants were divided into two eight-person panels. Primary data collection occurred on 22 December 1999 for the first panel and 4 January 2000 for the second panel. We arranged for participants to travel to the airport and clear security. We conducted continuous ambulatory ECG monitoring for 8 hr while participants alternated 2-hr periods in nonsmoking and smoking areas, beginning in the nonsmoking area. In both areas participants engaged in the same types of activities including mostly sitting while reading, visiting, playing cards, etc. Food and drinks were provided during each 2-hr time period, and participants were asked to eat similar amounts each time. During the middle of each 2-hr period, research personnel took food orders, purchased food from available airport vendors, and delivered it to the participants.

Participants completed activity diaries, including times when they moved from one area to another, ate, went to the restroom, or

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had any other significant change in activity. We created an activity index using information recorded in the diaries. It was simply the number of times that the individual ate or did something that required standing up and moving around, such as going to the restroom or getting up for a drink, in each 1.75-hr period. During the last 15 min of each 2-hr period the participants' blood oxygen saturation level (S_pO_2) was measured using a Nellcor N-20P portable pulse oximeter (Nellcor Inc., Hayward, CA). Participants could withdraw at any time if they became ill or uncomfortable, but all completed the study.

Air quality monitoring and exposure assessment. We conducted 2-hr integrated sampling alternately in the smoking and nonsmoking areas using samplers originally designed to monitor ETS on commercial aircraft. These samplers were self-contained in large briefcases and have been described

elsewhere (24). Nicotine (25) and RSP (with a cut point of $3 \mu m$ at the flow used in this study) were monitored at about the breathing zone while the participant was sitting. We used four ETS exposure variables in the analysis: a) a smoking area indicator variable; b) average number of lit cigarettes as counted every 5 min; c) nicotine concentrations; and d) RSP concentrations. We analyzed collected RSP for sulfate and determined concentrations of carbon monoxide, carbon dioxide, and nitrogen dioxide (24).

Ambulatory ECG monitoring and processing. At the airport, participants went to a private room and were hooked up to ambulatory ECG monitors by a trained technician. The hookup of a modified V_5 and aVF bipolar lead placement was used. Skin preparation, electrode placement, and related protocols were similar to those described elsewhere (26). Electrocardiograms were recorded digitally (sampling rate of 256 Hz

per channel) on removable flash cards using a light-weight, two-channel, ambulatory ECG monitor (Trillium3000, Forest Medical, East Syracuse, NY). The signal was recorded continuously throughout the study period. The ECG digital recordings were processed, and HR and HRV measures were calculated using PC-based software (Trillium3000 PC Companion Software for MS Windows, Forest Medical). Initially, beats were automatically detected and assigned tentative annotations, which were then thoroughly reviewed by an experienced scanner to correct for any mislabeled beats or artifacts. Only normal-to-normal beat (NN) intervals were included in the analysis.

The ECG recordings were divided into time periods in and out of the smoking area. For each 2-hr period, we deleted the first 10 min and the last 5 min in order to minimize the impact of disruptions and exposure misclassification associated with the transitional periods when participants moved to and from the nonsmoking and smoking areas. For each of the 1.75-hr time periods, we then calculated mean HR, five time-domain HRV measures, and five frequency domain HRV measures, as described in Table 1.

In practice, time-domain and frequency-domain measures are simply alternative approaches to measuring HRV. The time-domain calculations are easier to perform. Because of both mathematical and physiologic relationships, there is approximate correspondence between many of the time- and frequency-domain variables and they are, therefore, strongly correlated (10). For example, the time-domain measures Triangular Index and standard deviation of all NN intervals (SDNN) and the frequency-domain measure of total power are

Table 1. Time and frequency domain measures of HRV used in analysis.

Variable	Units	Description
Time domain measures		
Triangular Index		The total number of all NN intervals divided by the NN histogram height, an estimate of overall HRV.
SDNN	msec	The standard deviation of all NN intervals, an estimate of overall variability.
SDANN	msec	The standard deviation of all 5-min NN interval means, an estimate of long-term components of HRV.
SDNN Index	msec	The mean of all 5-min NN interval standard deviations, an estimate of variability due to cycles shorter than five minutes.
r-MSSD	msec	The square root of the mean of the squared differences between adjacent NN intervals, an estimate of the short-term components of variability.
Frequency domain measures		
Total	msec ²	Total power, frequency range < 0.4 Hz.
ULF	msec ²	Power in the ultralow frequency range (< 0.003 Hz).
VLF	msec ²	Power in the very low frequency range (0.003–0.04 Hz).
LF	msec ²	Power in the low frequency range (0.04–0.15 Hz).
HF	msec ²	Power in the high frequency range (0.15–0.4 Hz).

Table 2. Brief description of research subjects.

Subject	Age/race/sex	Smoking status	Medical summary	Prescription medication
1	37/black/M	Quit 3 years ago	Healthy	None
2	22/white/M	Never smoked	Healthy	None
3	66/white/M	Never smoked	Hypertension	Cimetidine, lisinopril, loratadine, cetirizine
4	22/white/M	Never smoked	Healthy	None
5	21/white/F	Never smoked	Healthy	Loratadine/pseudoephedrine, ibuprofen
6	21/white/F	Never smoked	Healthy	None
7	59/white/M	Never smoked	Asthma, borderline hypertension, diabetes	Pseudoephedrine/quaifenesis, inhaled fluticasone, albuterol, salmeterol, azelastine nasal spray, metformin, montelukast
8	46/white/F	Never smoked	Healthy	Estrogen
9	76/white/M	Never smoked	History of bronchitis, congenital renal disease, renal transplant in 1994, abnormal heart rhythm (premature depolarizations), hypothyroidism and diabetes	Cyclosporin-A, azathioprine, prednisone, levothyroxine, ranitidine
10	68/white/F	Never smoked	Shortness of breath walking uphill, history of abnormal heart rhythm, poor circulation in feet	None
11	35/white/F	Never smoked	Healthy	None
12	27/white/M	Quit 4 years ago	Healthy	None
13	30/white/F	Never smoked	Healthy	Oral contraceptive: levonorgestrel/ethinyl estradiol
14	60/white/M	Never smoked	Healthy	None
15	62/white/F	Never smoked	Healthy	None
16	68/white/M	Never smoked	Myocardial infarction, angioplasty, shortness of breath, angina, and congestive heart failure	Isosorbide, furosemide, warfarin, potassium chloride, nitroglycerine, losartan, carvedol, hydrocodone/acetaminophen

all measures of overall HRV and, therefore, are highly correlated. The time-domain measure r-MSSD (the square root of the mean of the squared differences between adjacent NN intervals) and the frequency-domain measure HF are both measures of the very short-term components of HRV and, therefore, are highly correlated.

We calculated frequency-domain measurements using power spectral analysis (10,27) following several approaches. First, a basic long-term analysis was conducted using a standard discrete Fourier transform algorithm, as described in detail elsewhere (28). We used all NN intervals in the 1.75-hr periods to determine the five frequency-domain measures described in Table 1. Next, each of these five components were reestimated after applying the Hamming window (28). Finally, we computed total, very low frequency (VLF), low frequency (LF), and high frequency (HF) for each 5-min interval, also applying the Hamming window. All of the 5-min interval values were then averaged across the 1.75-hr periods. Correlations between the basic long-term frequency domain estimates and those applying the Hamming window for total, ultralow frequency (ULF), VLF, LF, and HF were high at 0.96, 0.88, 0.98, 0.98, and 0.98, respectively. Correlations between measures of VLF, LF, and HF using the basic long-term frequency domain estimates versus averages of 5-min intervals were also high at 0.98, 0.99, and 0.98, respectively. Because the estimates from these three approaches were so closely correlated, the

statistical analysis of HRV and ETS exposure focused on the time-domain and basic long-term frequency domain HRV measures.

Statistical analysis. Initially, we conducted simple comparative statistics including estimating relevant cross-correlation coefficients and plotting measures of HRV

against exposure variables. Associations with ETS were evaluated statistically using pooled data and fixed-effects regression modeling techniques (29). The basic regression models for the HRV measures included one of the ETS exposure variables, 16 subject-specific indicator variables, and a time-period variable

Table 4. Pearson correlation coefficients between various HR and HRV variables (n = 64).

	Mean HR	Triangular Index	SDNN	SDANN	SDNN Index	r-MSSD
Triangular Index	-0.48	1.00	0.86	0.76	0.86	0.29
SDNN	-0.71	0.86	1.00	0.82	0.93	0.66
SDANN	-0.57	0.76	0.82	1.00	0.62	0.31
SDNN Index	-0.63	0.86	0.93	0.62	1.00	0.63
r-MSSD	-0.58	0.29	0.66	0.31	0.63	1.00
Total	-0.64	0.82	0.94	0.80	0.85	0.60
ULF	-0.55	0.78	0.83	0.96	0.64	0.31
VLF	-0.55	0.91	0.81	0.63	0.87	0.25
LF	-0.51	0.72	0.82	0.51	0.82	0.62
HF	-0.46	0.30	0.60	0.34	0.52	0.79

All correlation coefficients > 0.35 were statistically significant at p < 0.01.

Table 3. Mean values of variables used in primary analysis during periods in and out of the smoking area.

Variable description	Mean values	
	Nonsmoking area (n = 32)	Smoking area (n = 32)
Exposure variables		
No. of cigarettes	0.0	8.77
Nicotine (µg/m ³)	0.43	34.03
RSP (µg/m ³)	24.74	77.97
CO (ppm)	0.85	1.32
Activity index	1.94	1.63
Time domain HR, HRV		
Mean HR (bpm)	77.63	79.39
Triangular Index	21.02	17.14
SDNN (msec)	80.41	68.91
SDANN (msec)	46.78	36.41
SDNN Index (msec)	57.31	52.03
r-MSSD (msec)	47.88	44.56
Frequency domain HRV		
Total (msec ²)	3,510	2,474
ULF (msec ²)	1,567	954
VLF (msec ²)	932	734
LF (msec ²)	565	446
HF (msec ²)	446	341
LF/HF	2.45	2.44
Oxygen saturation		
S _p O ₂ (%)	96.68	96.34

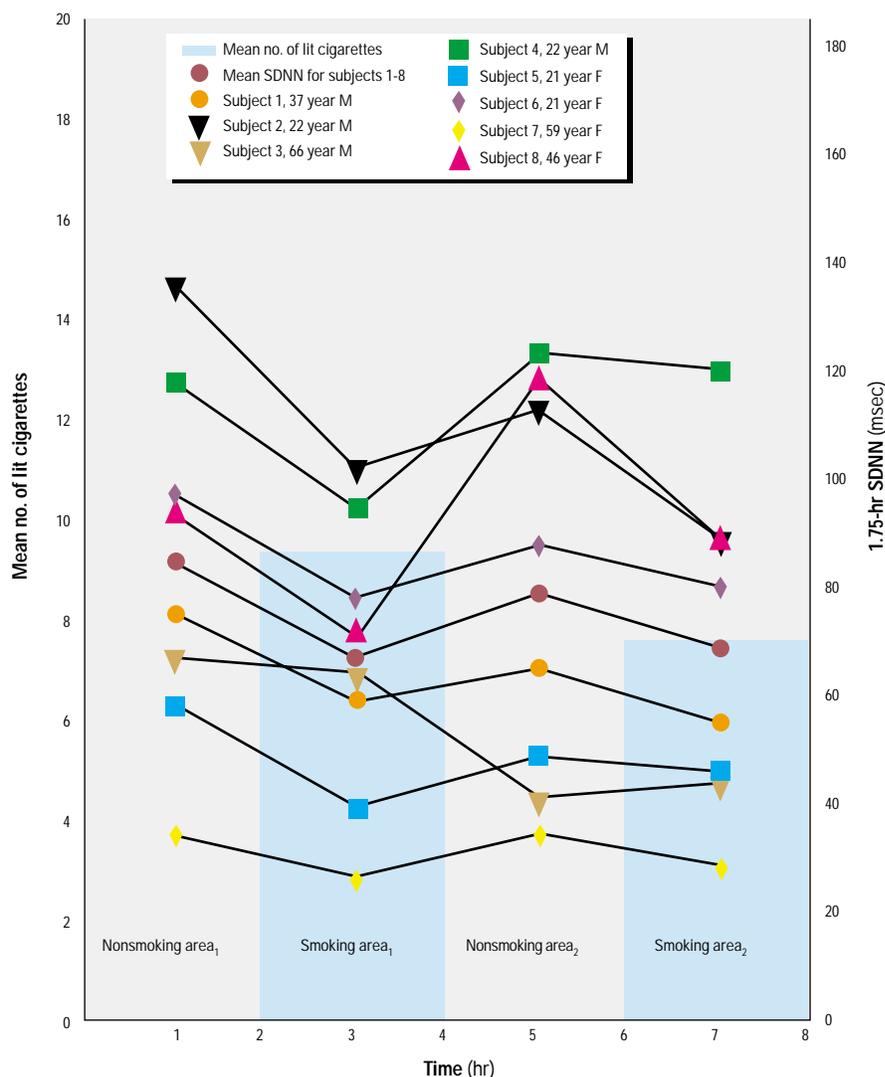


Figure 1. SDNN for subjects 1–8 and the mean SDNN across these subjects plotted over the 8 hr of the study period and ETS exposures (22 December 1999, 1015–1815 hr). Nicotine and RSP concentrations, respectively, were 0 µg/m³ and 43 µg/m³ for nonsmoking area₁, 23 µg/m³ and 166 µg/m³ for smoking area₁, 2 µg/m³ and 26 µg/m³ for nonsmoking area₂, and 38 µg/m³ and 57 µg/m³ for smoking area₂.

(1–4 corresponding to the four 2-hr exposure periods) that allows for trending throughout the 8-hr study period. Further analysis included the estimation of models with other variables such as the activity index and previous period RSP exposure. We estimated autoregressive models that allowed for first-order nonindependent error terms using a maximum likelihood method (30). Models stratified for each of the 16 participants and specific subgroups were also estimated.

Results

Table 2 provides a description of the research subjects including nine men and seven women ranging from 21 to 76 years of age. Most were relatively healthy, but some had a history of respiratory and/or cardiovascular disease. All of the subjects were non-smokers. Two had quit smoking 3 or 4 years prior to the study. Comparisons of mean values of key variables are presented in Table 3. Nicotine and RSP levels were substantially higher in the smoking area. Average physical activity levels were slightly lower during smoking area periods, but mean HR was 1.76 beats/min higher. Measures of HRV were consistently lower during periods in the smoking area. Table 4 presents cross-correlation coefficients between the HR and HRV variables. Mean HR was negatively correlated with all measures of HRV. SDNN was most highly correlated with measures of overall HRV and estimates of the longer-term components of variability, but SDNN was also highly correlated with estimates of short-term components of variability such as r -MSSD ($r = 0.66$) and HF ($r = 0.60$).

Figures 1 and 2 present subject-specific SDNN measures plotted over the study period. Exposure periods, average number of cigarettes smoked, and nicotine and RSP concentrations are also indicated. Data collection for the first panel occurred when the airport was relatively more crowded due to elevated preholiday traffic. RSP concentrations (but not nicotine or number of smokers) were higher for the first panel—both in and out of the smoking area. Most of the variability in HRV was due to differences across individuals. For the majority of the subjects, SDNN tended to decline after they moved into the smoking area, recover when they returned to the nonsmoking area, and then decline again when they moved back to the smoking area. A subtle decline in SDNN through the study period may be part of a diurnal pattern or be suggestive that the subjects do not fully recover after the first ETS exposure.

Table 5 shows the estimated regression coefficients between HR and HRV measures and ETS exposure variables. The regression models also included 16 subject-specific indicator (fixed-effects) variables and a time-trend

variable. For the HRV models, mean heart rate was also included as a covariate. Mean HR was not significantly associated with ETS. All of the HRV measures were consistently negatively associated with all four ETS exposure variables. Associations with measures of overall HRV and measures of long-term components of variability were more strongly associated with ETS than were estimates of the short-term components of variability. The LF/HF ratios were not significantly associated with ETS exposure, nor was S_pO_2 .

Table 6 shows estimated regression coefficients between SDNN and the ETS exposure variables for models controlling for different combinations of covariates. Estimated associations between HRV and ETS exposure were not sensitive to controlling for other nonexposure variables (Models 1–5). The

autoregressive term was generally not statistically significant and had little impact on the ETS effect estimates (Model 6). Mean HR was often significantly associated with HRV. The regression coefficient (standard error) for the mean HR variable, based on Model 3 in Table 6 using RSP as the exposure variable, was -0.87 (0.45 , $p = 0.06$). The activity index and lagged PM values were never statistically significant ($p > 0.15$).

Subject-specific regressions indicated that the associations between SDNN and ETS variables were consistently negative for all but two of the subjects. These two subjects included subject 3, a medicated hypertensive male, and subject 9, a diabetic male who had a renal transplant and was taking the immunosuppressant cyclosporin-A. Regression models were estimated following stratification by subject and specific

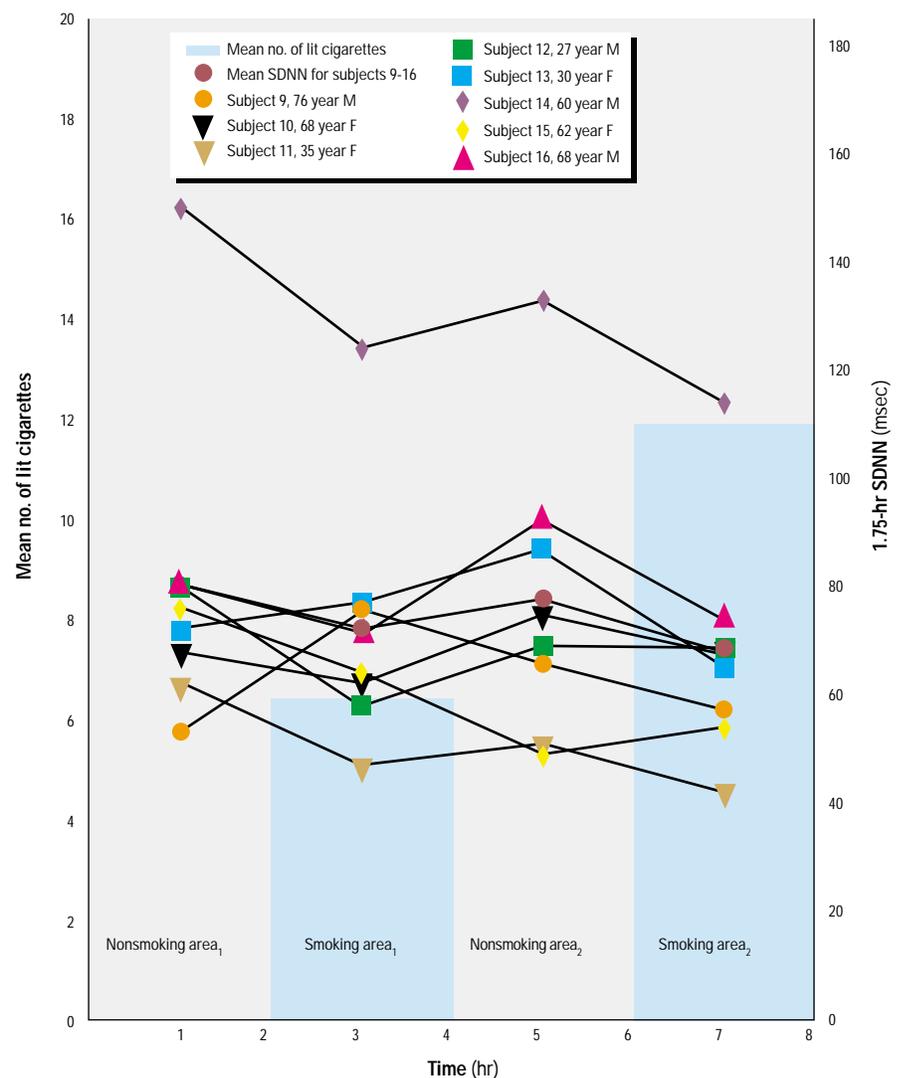


Figure 2. SDNN for subjects 9–16 and the mean SDNN across these subjects plotted over the 8 hr of the study period and ETS exposures. (4 January 2000, 0945–1745 hr). Nicotine and RSP concentrations, respectively, were $0 \mu\text{g}/\text{m}^3$ and $18 \mu\text{g}/\text{m}^3$ for nonsmoking area₁, $21 \mu\text{g}/\text{m}^3$ and $41 \mu\text{g}/\text{m}^3$ for smoking area₁, $0 \mu\text{g}/\text{m}^3$ and $12 \mu\text{g}/\text{m}^3$ for nonsmoking area₂, and $53 \mu\text{g}/\text{m}^3$ and $48 \mu\text{g}/\text{m}^3$ for smoking area₂.

subgroups. No clear differences were observed across former smoking status and age. The association between SDNN and ETS exposure was greater for females than for males, but the difference was greatly attenuated excluding subjects 3 and 9.

Discussion

Although numerous epidemiologic investigations have shown associations between ETS exposure and cardiovascular disease (1–8), the pathophysiologic pathways need further exploration. There has been growing recognition of the importance of the autonomic nervous system in cardiovascular disease (10). Deleterious health outcomes associated with reduced cardiac autonomic function, as measured by time-domain and frequency-domain measures of HRV, has been well established (10–12,31). Parallel research has observed associations between exposure to combustion-related RSP from outdoor origin and cardiopulmonary disease similar to associations observed with ETS (19–23). A few recent studies have shown that acute changes

in exposure to RSP primarily from outdoor origin are associated with short-term changes in HR (15) and HRV (16–18). These findings have led to speculation that alterations in cardiac autonomic control may represent an important pathophysiologic mechanism by which RSP lead to cardiac mortality (31).

Given that ETS is a primary source of RSP exposure in many indoor environments, in this study we explored effects of short-term ETS exposure on changes in cardiac autonomic function. We evaluated realistic, real-world exposures to ETS by using smoking areas in a commercial airport. Nicotine and RSP concentrations observed during exposure periods in this study were comparable to concentrations common to many workplace environments (32). In this study we observed consistent decrements in HRV associated with ETS exposure. Measures of overall HRV and measures of long-term components of variability were more strongly associated with ETS than were estimates of the short-term components of variability. These results were quite robust, with similar

results being observed across various strata, modeling approaches, and measures of HRV.

It is unclear which constituents of ETS are responsible for the apparent effect on HRV. It is unlikely that CO was primarily responsible because the CO concentrations were extremely low. The elevated nicotine levels may play a role; however, in a recent study of much higher nicotine exposure through nicotine patch administration, only minor changes in autonomic regulation were found (33). The estimated HRV associations with RSP observed in this study are somewhat comparable with those from recent air pollution studies. A study of 26 elderly subjects living in metropolitan Baltimore, Maryland, (16) observed that 6-min SDNN, LF, and HF were negatively associated with ambient and indoor particulate pollution. In a second air pollution study (17), weekly ECG monitoring was conducted continuously for 25 min in a controlled setting on 21 53–87 year-old subjects in Boston, Massachusetts. Although RSP concentrations never exceeded 50 $\mu\text{g}/\text{m}^3$, based on the reported regression coefficients, a 100- $\mu\text{g}/\text{m}^3$ increase in 4-hr RSP exposure was associated with approximately a 25-msec decline in both SDNN and r-MSSD.

Another air pollution study conducted repeated 24-hr ambulatory ECG monitoring on seven subjects in Utah during periods of high and low ambient air pollution (18).

SDNN and SDANN (but not r-MSSD) were significantly negatively associated with particulate air pollution. The estimated decline in 24-hr SDNN associated with 100 $\mu\text{g}/\text{m}^3$ in PM_{10} was approximately 18 msec (SE = 4.9). In this ETS study, the estimated decline in 1.75-hr SDNN associated with 100 $\mu\text{g}/\text{m}^3$ in RSP was approximately 11 msec. Such comparisons of estimated effects on HRV are not fully accurate because of differences in exposure sources, exposure measurements, and time frame of ECG monitoring. Nevertheless, the estimated RSP effects on HRV are somewhat consistent. Also, consistent with the recent air pollution studies, this study suggests that the effect of exposure to ETS on HRV occurs rapidly and is largely transient.

A recent prospective study of HRV and mortality with chronic heart failure patients was conducted by Nolan et al. (12). The relative risk associated with a 41.2-msec decrease in SDNN (from 24-hr ambulatory ECG monitoring) was 1.62 [95% confidence interval (CI), 1.16–2.44]. By back-calculating the proportional hazard regression coefficient from Nolan et al. (12) and using our estimated reduction in SDNN from ETS exposure from this study, an interesting plausibility check can be made. The estimated average decline in SDNN associated

Table 5. Estimated regression coefficients (standard errors) between HR and HRV measures and the ETS exposure variables.

Variable	Regression coefficients for exposure variables			
	Smoking area indicator	No. cigarettes ($\times 10$)	Nicotine ($50 \mu\text{g}/\text{m}^3$)	RSP ($100 \mu\text{g}/\text{m}^3$)
Mean HR (bpm)	0.66 (0.85)	0.25 (0.97)	-0.23 (1.37)	0.38 (0.95)
Triangular Index	-3.44 (0.84) [#]	-3.46 (0.98) [#]	-4.16 (1.44) [#]	-3.50 (0.96) [#]
SDNN (msec)	-9.61 (2.67) [#]	-11.08 (2.97) [#]	-13.71 (4.35) [#]	-11.08 (2.92) [#]
SDANN (msec)	-9.22 (3.46)**	-10.86 (3.85) [#]	-13.08 (5.58)**	-10.90 (3.78) [#]
SDNN Index (msec)	-4.40 (1.87)**	-5.05 (2.10)**	-6.34 (3.00)**	-5.49 (2.04) [#]
r-MSSD (msec)	-2.58 (3.23)	-4.01 (3.61)	-4.93 (5.11)	-3.85 (3.56)
Total (msec ²)	-878 (250) [#]	-1,043 (276) [#]	-1,340 (400) [#]	-1,000 (274) [#]
ULF (msec ²)	-526 (204)**	-614 (227) [#]	-725 (329)**	-649 (221) [#]
VLF (msec ²)	-146 (57.9)**	-149 (66)**	-198 (94)**	-163 (64)**
LF (msec ²)	-107 (47.1)**	-132 (52)**	-181 (74)**	-110 (53)**
HF (msec ²)	-99.3 (76.7)	-148 (85)*	-235 (119)*	-78 (86)
LF/HF	-0.12 (0.19)	-0.08 (0.21)	-0.14 (0.30)	-0.05 (0.21)
S _p O ₂ (%)	-0.08 (0.25)	-0.01 (0.28)	0.19 (0.40)	-0.23 (0.27)

Models also include 16 indicator (fixed effects) variables for each individual, and a "time-trend" variable (1–4) indicated the time period. Also for all the HRV models, mean heart rate is included as a variable in the models.

*, **, and [#] indicate $p \leq 0.10$, 0.05, and 0.01, respectively; p -values are based on two-tailed t -tests and indicate the probabilities for testing the null hypothesis that the parameter is not significantly different from zero.

Table 6. Estimated regression coefficients (SEs) between SDNN and the ETS exposure variables for models that control for different covariates.

Other variables included in the model	Regression coefficients for exposure variables			
	Smoking area indicator	No. cigarettes ($\times 10$)	Nicotine ($50 \mu\text{g}/\text{m}^3$)	RSP ($100 \mu\text{g}/\text{m}^3$)
Model 1. Subject indicator	-11.50 (2.43) [#]	-12.54 (2.62) [#]	-14.02 (3.28) [#]	-10.91 (3.30) [#]
Model 2. Subject indicator, time period	-10.13 (2.71) [#]	-11.30 (3.07) [#]	-13.48 (4.52) [#]	-11.41 (3.00) [#]
Model 3. Subject indicator, time period, mean HR	-9.61 (2.67) [#]	-11.08 (2.97) [#]	-13.71 (4.35) [#]	-11.08 (2.92) [#]
Model 4. Subject indicator, time period, mean HR, activity index	-9.63 (2.82) [#]	-11.20 (3.16) [#]	-13.60 (4.59) [#]	-11.35 (3.13) [#]
Model 5. Subject indicator, time period, mean HR, activity index, lagged RSP	-10.01 (3.57) [#]	-11.58 (3.93) [#]	-14.41 (6.29)**	-10.60 (3.42) [#]
Model 6. Subject indicator, time period, mean HR, autoregressive term	-9.59 (3.17) [#]	-10.72 (3.44) [#]	-12.95 (5.18)**	-10.39 (3.25) [#]

*, **, and [#] indicate $p \leq 0.10$, 0.05, and 0.01, respectively; p -values are based on two-tailed t -tests and indicate the probabilities for testing the null hypothesis that the parameter is not significantly different from zero.

with ETS exposure in the airport was approximately 10 msec. Based on the results from Nolan et al. (12), the estimated relative mortality risk of a 10-msec decline in SDNN can be calculated as $1.12 \{e^{10 \times (\ln 1.62)/41.2}\}$. Lack of compatibility between these studies, such as SDNN calculations for different periods, make comparing relative risk estimates highly imprecise. Nevertheless, this estimated risk ratio seems somewhat plausible with an estimated excess risk about one-half as large as the total ETS-related excess risk as observed directly from epidemiologic studies. Meta-analyses of coronary events among never-smokers who are married to smokers compared to those married to nonsmokers or exposed to ETS in the workplace yield combined average relative risks of 1.25 (95% CI, 1.17–1.33) (6) and 1.21 (95% CI, 1.04–1.41) (34), respectively. The total ETS-related excess risks directly observed in the epidemiologic studies are expected to be larger because elevated exposure in this study was only short term, whereas workplace- and spousal-related exposures are long term. Furthermore, altered cardiac autonomic control is likely only one of multiple mechanistic links between ETS exposure and cardiovascular disease mortality (9).

Mechanistic hypotheses by which respirable particles affect neural control of the heart have been proposed (31). Also, some recent animal studies suggest that increased cardiac vulnerability does not occur through hypoxia, but through changes in cardiac autonomic function (35). Mechanistic pathways by which ETS and other respirable particles may affect cardiac autonomic function and risk of cardiovascular disease, however, clearly need further exploration.

Although the associations between ETS exposure and various measures of HRV observed in this study were quite robust and statistically significant, the basic observations of this study need to be replicated. This study, nonetheless, suggests that altered cardiac autonomic function, as reflected by decrements in HRV, may be part of the pathophysiological mechanisms by which

exposure to ETS (and possibly other combustion-related particulate pollutants) leads to increased risk of cardiovascular mortality.

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